

REVIEW

Insulin resistance as a contributor to myocardial ischaemia independent of obstructive coronary atheroma: a role for insulin sensitisation?

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There is good evidence to suggest that insulin resistance and its surrogate markers are at least modest independent cardiovascular risk factors. However, as well as long term effects on atheromatous coronary disease, there is a well described correlation between markers of insulin resistance and endothelial dysfunction. In this review, the evidence for a relation between endothelial dysfunction and myocardial ischaemia is summarised. The evidence for a correlation between insulin resistance and endothelial dysfunction and the proposed cellular mechanisms are also examined. Finally, the potential role for insulin sensitising strategies is looked at and recent data examining their effects on both endothelial function and clinical symptoms is examined. In conclusion, it was found that insulin sensitising modalities have a potential role in the amelioration of angina and that randomised controlled studies are therefore warranted.

Here we collate available evidence to suggest that insulin resistance, in addition to promoting physical obstructive atheromatous coronary disease, may lead to myocardial ischaemia via the process of endothelial dysfunction. Based on these observations, we suggest that amelioration of insulin resistance, whether by established or novel mechanisms, may at least in part restore normal endothelial function and potentially ameliorate anginal symptoms.

Evidence for endothelial dysfunction as a causative factor in angina independent of obstructive disease

In conventional angina there is evidence to suggest that endothelial function in the myocardial vascular bed is abnormal. Coronary atherosclerosis is associated with a reduced vasodilator response and a paradoxical vasoconstrictor response to acetylcholine. This has been shown in response to both atrial pacing and bicycle exercise during coronary angiography and these functional abnormalities may contribute to ischaemia in patients with obstructive coronary disease.^{3–5} However, it is difficult to implicate this as a direct cause of ischaemia caused by co-existing flow limiting atheroma.

A subgroup of patients with angina has normal coronary arteries despite evidence of ischaemia demonstrated using non-invasive methods. This defines the group termed to have microvascular angina. There is good evidence to support the notion that these patients also have impaired microvascular function mediated by abnormal endothelial vasomotor responses and that this could potentially be an aetiological factor in ischaemia. Impaired endothelial function has been demonstrated in subjects with “cardiac syndrome X”, using methods including brachial artery flow mediated dilatation^{6,7} and abnormal coronary vascular responses assessed by intracoronary Doppler.^{8,9} In fact, recent data published in abstract form support a correlation between levels of endothelial dysfunction and ST segment depression as a marker for ischaemia in such women.¹⁰

It is postulated that this impairment of endothelial function results in failure of the normal coronary vasodilatory response at times of stress, such that the arterial supply does not match the enhanced demand, leading to the activation of anaerobic metabolism and

Myocardial ischaemia is a common cause of morbidity and mortality. Essentially, ischaemia occurs when the blood supply to the myocardium is too poor for its metabolic demands to be met. The end artery nature of the coronary circulation, with a relative lack of anastomosis between the major coronary arteries, makes the condition more prevalent in myocardium. When the myocardial metabolic demands, in particular for oxygen, are not met, anaerobic metabolism manifests, with production of lactate, leading to symptomatic angina. At its most serious, myocytes that remain ischaemic beyond a critical time period die, resulting in myocardial infarction.

The importance of type 2 diabetes mellitus is well established as a cardiovascular risk factor. The cardiovascular risk of patients with insulin resistance, with or without glucose intolerance, has become apparent as described in a recent meta-analysis, looking at hyperinsulinaemia as a surrogate marker.¹ Reaven described the forerunner of what has become known as insulin resistance syndrome (also called metabolic syndrome X) in 1988. Since then, the definitions have been extended such that a cluster of interrelated cardiovascular risk factors including central adiposity, hypertension, dyslipidaemia, and disturbances of fibrinolysis, with abnormalities of insulin metabolism at the core, are now described.²

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Abbreviations: NO, nitric oxide; PI3-kinase, phosphatidylinositol 3-kinase

Table 1 Summary of intervention trials looking at insulin sensitisers and outcomes of endothelial function and symptoms

Author	Species	Population	Design	Total numbers	Drug	Period	Insulin resistance	Vascular function	Angina
Walker <i>et al</i> ⁴⁹	Rat	Fatty, Zucker rats	Controlled, parallel treatment	n = 16	Rosiglitazone 50 µmol/kg	9–12 weeks	Improved (fasting hyperinsulinaemia)	Improved (ex-vivo myography)	
Verma <i>et al</i> ⁴¹	Rat	Fructose-induced hypertensive rats	Two parallel treatment groups (non-controlled)	n = 21	Metformin 500 mg/kg/day	8 weeks	Improved (fasting serum insulin/glucose)	Improved (reactivity of aorta ex vivo)	
Vehkavaara <i>et al</i> ²⁸	Human	Type 2 diabetes on metformin	Controlled, parallel treatment	n = 24	Insulin	6 months		Improved (venous occlusion plethysmography)	
Mather <i>et al</i> ³⁹	Human	Type 2 diabetes (diet controlled)	Placebo controlled	n = 44	Metformin 500 mg twice daily	12 weeks	Improved (HOMA-IR)	Improved (forearm plethysmography)	Reduced symptoms and fewer MI
Sgambato <i>et al</i> ⁵³	Human	Post-MI (mixed glucose tolerance)	Controlled (no placebo) and non-randomised	n = 310	Metformin 1–2 g/day	3 years			Improved treadmill Duke score
Jadhav <i>et al</i> ⁴⁰	Human	Women with cardiac syndrome X	Double blind, randomised, placebo controlled	n = 46	Metformin 500 mg twice daily	8 weeks	Improved (fasting serum insulin)	Improved (laser Doppler imaging)	
Watanabe <i>et al</i> ⁴⁶	Human	Non-diabetic hyperinsulinaemic males	Two parallel treatment groups	n = 15	Troglitazone 400 mg/day	4 weeks	Improved	Improved (brachial artery ultrasound)	
Tack <i>et al</i> ⁵⁰	Human	Obese	Randomised, double blind, crossover	n = 15	Troglitazone 400 mg/day	8 weeks	Improved	No change (venous occlusion plethysmography)	
Pampaloni <i>et al</i> ⁴⁸	Human	Insulin resistant, non-diabetic	Non-controlled	n = 9	Troglitazone 600 mg/day	3 months	Improved (glucose clamping)	Improved (cold pressor test using PET)	Reduced anginal episodes and use of nitrates
Murakami <i>et al</i> ⁵¹	Human	Diabetic with vasospastic angina	Non-controlled	n = 10	Troglitazone 400 mg/day	4 months	Improved (fasting hyperinsulinaemia)	Improved (brachial artery ultrasound)	Improved treadmill effort tolerance
Murakami <i>et al</i> ⁴⁷	Human	Type 2 diabetes with angina	Randomised, controlled parallel treatment	n = 22	Troglitazone 400 mg/day	4 months	Improved (HOMA index)	Improved (brachial artery ultrasound)	

HOMA-IR, homeostasis model assessment-insulin resistance; MI, myocardial infarction; PET, positron emission tomography.

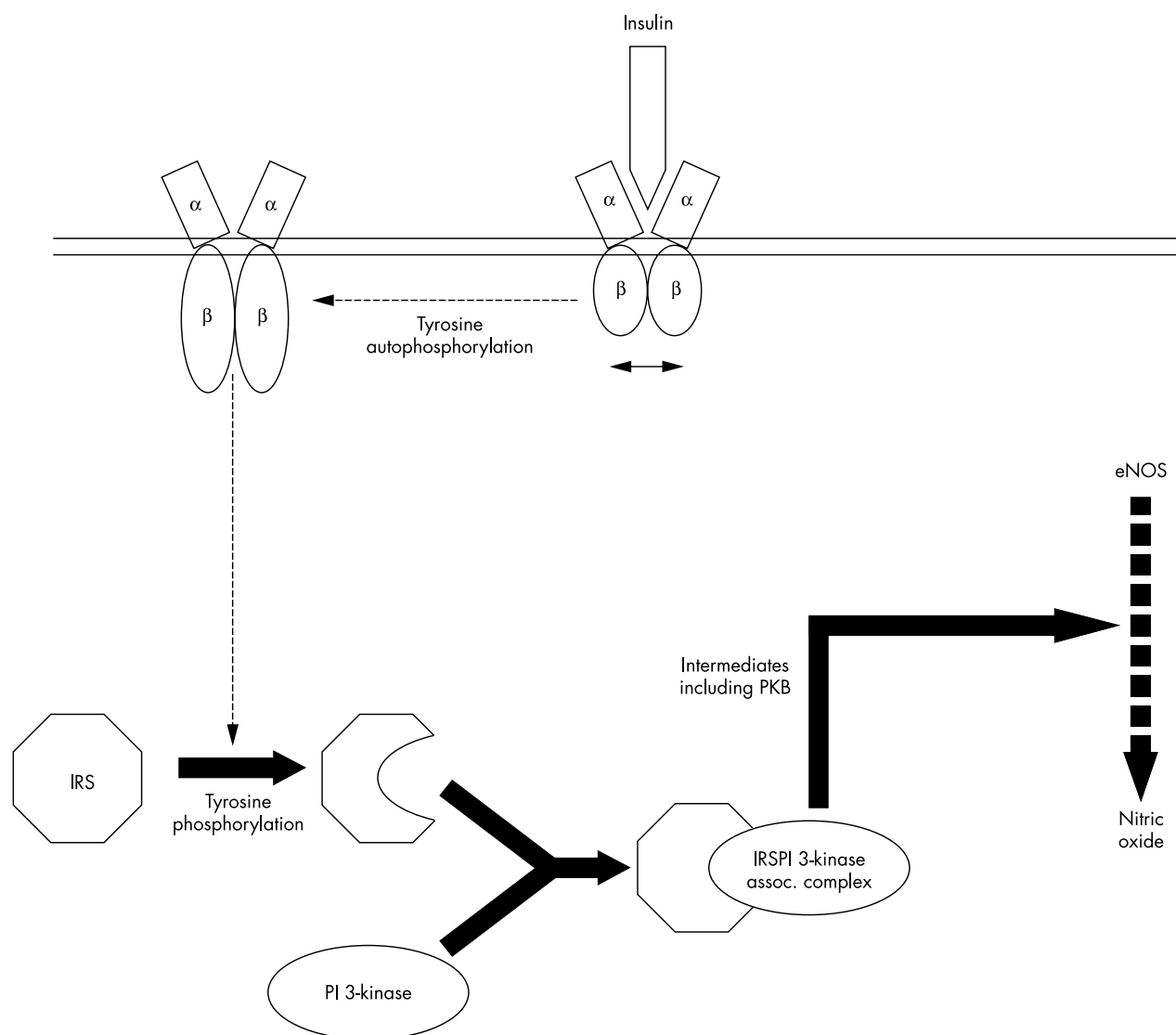


Figure 1 Schematic outlining insulin receptor and nitric oxide production coupling in endothelium. eNOS, endothelial nitric oxide synthase; IRS, insulin receptor substrate; PI 3-kinase, phosphatidylinositol 3-kinase; PKB, protein kinase B.

ischaemic pain. This group of patients provides an opportunity to study functional vessel abnormalities in the absence of obstructive atheroma.

Link between insulin resistance and endothelial dysfunction

Insulin resistance, as well as being the precursor for type 2 diabetes, has several pleiotrophic effects. These include several of the features of the metabolic syndrome including dyslipidaemia, as well as direct promotion of atheroma production.

Another such effect is its influence on vascular function. Impaired endothelial function in type 2 diabetes has been shown using venous occlusion plethysmography,^{11 12} high resolution brachial artery ultrasound,¹³ and more recently by laser Doppler imaging.¹⁴ In addition, Balletshofer *et al* have shown that clamp derived indices of insulin resistance correlate with endothelial responses in first degree relatives of subjects with type 2 diabetes, using brachial artery ultrasound.¹⁵ Similarly, Jaap *et al* described an association between insulin sensitivity and microvascular function in non-diabetic subjects with fasting hyperglycaemia, using laser Doppler fluximetry in response to local heating.¹⁶ Serne

et al extended these observations by demonstrating that microvascular function as assessed by laser Doppler flowimetry is associated with insulin sensitivity even in normal subjects.¹⁷ Furthermore, in a study of the coronary circulation in subjects with unobstructed coronaries, a strong correlation between clamp derived indices of insulin resistance and coronary vascular function assessed by Doppler blood flow recordings was noted.¹⁸

Other aspects of the insulin resistance syndrome have been associated with endothelial dysfunction. Obese individuals without diabetes have endothelial dysfunction both in the peripheral and coronary circulation,¹⁹ and a specific link to central adiposity has been noted by some.²⁰ Steinberg *et al* showed blunted leg blood flow in response to arterial infusions of methacholine in obese, insulin resistant subjects compared to controls. Importantly, whereas the production of euglycaemic hyperinsulinaemia augmented blood flow in lean subjects, this response was not apparent in obese.²¹ Endothelial dysfunction has also been documented in vivo and ex vivo experiments in subjects with hypertension, and in association with dyslipidaemia, particularly in those subjects with high triglycerides and low high density lipoprotein (HDL) cholesterol.^{22–24}

A close correlation between insulin sensitivity and endothelial nitric oxide (NO) synthesis is seen in healthy volunteers.²⁵ A similar correlation is seen between insulin sensitivity and vasoconstrictor responses to N-monomethyl-L-arginine, a NO inhibitor, in a mixed group of men including patients with diabetes, hypertension, and healthy volunteers.²⁶ Furthermore, the vasodilatory effect of insulin is amplified in the presence of metabolically active glucose in healthy subjects.²⁷ This observation, together with findings that insulin augments blood flow in lean subjects, points towards a key role for insulin and glucose metabolism in maintaining vasodilator tone in vessels via NO. This is supported by the observation that exogenous insulin treatment appears to improve endothelial function in patients with type 2 diabetes.²⁸

The post-receptor signalling mediators involved in the production of NO in response to insulin in many ways parallel those which regulate insulin mediated glucose transport via GLUT4 translocation (fig 1). It appears that activation of phosphatidylinositol 3-kinase (PI3-kinase) is crucial in this signalling pathway. Cells expressing an inhibitory mutant of PI3-kinase have a much attenuated NO response to insulin. Downstream mediators of this effect may include protein kinase B (PKB) also known as Akt.²⁹ possibly by phosphorylating endothelial nitric oxide synthase (eNOS).³⁰ However, other pathways may also be involved and remain to be characterised. In particular, intracellular Ca^{+2} concentrations are affected by insulin, mainly by stimulation of the $\text{Na}^{+}\text{-H}^{+}$ exchanger and $\text{Na}^{+}\text{-K}^{+}$ ATPase and therefore insulin resistance may have a direct Ca^{+2} mediated influence on vascular tone.³¹

Microvascular angina, insulin resistance, and endothelial dysfunction

In parallel with the above observations, several groups have demonstrated relative insulin resistance in post-menopausal women and non-obese men with microvascular angina, together with lipid perturbances and higher blood pressure.^{32–36}

Furthermore, there are data to suggest that subjects with microvascular angina have a reduced whole body NO response to insulin.³⁷ This leads to the hypothesis that resistance to this effect of insulin could manifest in impaired endothelial function via intermediates including NO.

Can improving insulin resistance improve endothelial function?

While the above observations are compelling, proving a causal relation between insulin action and endothelial function requires interventional studies. Very recent uncontrolled data show that intentional weight loss by means of a hypocaloric diet combined with exercise, and in some cases surgical liposuction, improves endothelial vasomotor function as measured by haemodynamic responses to intravenous L-arginine (a NO precursor).³⁸ This improvement coincided with reduction in fasting insulin and cytokine concentrations.

Metformin, the only biguanide in clinical use, has been available in the UK for over 30 years. Its exact mechanism of action remains unclear but it is thought to involve increasing tyrosine kinase activity in the insulin receptor with intracellular effects mediated via the PI3-kinase pathway on GLUT4 translocation as well as NO production (fig 1).

One 12 week trial of metformin compared to placebo in individuals with type 2 diabetes showed improved endothelial function as measured by forearm plethysmography, in the metformin group alone.³⁹ Data recently published in abstract form reported significant improvements in endothelial dependant microvascular function, in a group of women with cardiac syndrome X, following eight weeks of metformin treatment compared with placebo.⁴⁰ These observations concur with preliminary animal data where chronic

metformin treatment improved aortic vascular properties in hyperinsulinaemic, fructose induced hypertensive rats.⁴¹ Metformin has other complex intracellular actions, one of which is activation of adenylyl monophosphate kinase (AMP-kinase),⁴² which in turn has been shown to directly activate NO synthase.⁴³ This mechanism in itself may contribute to the vasoactive effects of metformin independently of its action on insulin metabolism.

Modest weight loss during metformin treatment is well described⁴⁴ and thus it is difficult to dissect whether vascular effects are solely because of this. By contrast, thiazolidinediones improve insulin sensitivity without reducing weight, with redistribution of adipose tissue from visceral to subcutaneous deposits.⁴⁵ Troglitazone has been reported to improve endothelial function measured by flow mediated brachial artery diameter, after either four weeks⁴⁶ or four months of treatment.⁴⁷ Preliminary data have extended these findings to include an improvement in myocardial blood flow, measured non-invasively using positron emission tomography, in non-diabetic insulin resistant individuals after three months of troglitazone treatment.⁴⁸ In animal models, rosiglitazone improved indices of insulin resistance and myography based measures of vascular function in fatty Zucker rats.⁴⁹ There is one report, however, showing a lack of effect of troglitazone on vascular function assessed by plethysmography.⁵⁰

Can improving insulin resistance lessen anginal frequency?

Preliminary data suggests that in diabetic patients with angina, four months treatment with troglitazone not only improves endothelial function, as assessed by brachial artery ultrasound, but also treadmill exercise capacity.⁴⁷ In a study published so far only in abstract form, troglitazone has also had beneficial effects on both the frequency of chest pain, and measures of endothelial function, in vasospastic angina,⁵¹ which is associated with insulin resistance and abnormal vascular function.⁵² Another study, also only in abstract form so far, demonstrated improved Duke score ischaemic measures in women with cardiac syndrome X following metformin administration.⁴⁰ Finally, a non-randomised study of metformin, given post-myocardial infarction, to a large group of patients with varying glucose tolerance, suggested a significant lessening of anginal symptoms and fewer new infarcts in those who received metformin compared to those who did not.⁵³

CONCLUSION

Prospective data have established markers of insulin resistance as an independent cardiovascular risk factor. We have suggested that insulin resistance is implicated in the pathogenesis of endothelial dysfunction, and therefore via this route, myocardial ischaemia. Indeed, there is tantalising evidence to show that insulin sensitisers may improve not only insulin resistance and endothelial function, but also anginal symptoms and exercise capacity in diverse patient groups. We suggest, therefore, that further properly randomised studies are required to elaborate the potential of insulin sensitising agents in the treatment of angina.

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